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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,554	10/06/2000	John F. Engelhardt	875.024US1	4157

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,554	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 8-11* is/are pending in the application.

4a) Of the above claim(s) *2,3,8,10,11,21,23-37,41-43,48-54,62 and 65* is/are withdrawn from consideration.

5)☒ Claim(s) *60 and 61* is/are ~~allowed~~. allowable

6)☒ Claim(s) *1,9,19,20,46,47,58 and 59* is/are rejected.

7)☒ Claim(s) *63,64,66 and 67* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/5/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed August 19, 2005 in response to the Office Action of February 25, 2005 is acknowledged and has been entered. Claims 1, 9, 19, 20, 46, 47, 58-61, 63, 64, 66, 67 are pending and are currently being examined. Please note in the prior Office action claim 47 was included as being examined, however, claims 47 is dependent on claim 25 which belongs in the nonelected Group I, thus claim 47 should not have been included with the instant claims. Claims 62, and 65 are drawn to enhancers which belong into Group III.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claims 58 and 59 (note claim 57 has been deleted in the instant amendment) under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is withdrawn** because the claim amendment to claim 1 and claim 19 make it clear that the entire open reading frame for the therapeutic gene product if encoded by a second AAV.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 9, 46 under 35 U.S.C. §102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1) **is withdrawn** in view of Applicants arguments and amendments to the claim. The claims are now drawn to a composition comprising two

rAAV constructs in which one of the constructs contains the entire open reading for a therapeutic gene construct.

The rejection of claims 47 are under 35 U.S.C. §102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1) **is maintained** for reasons of record. In this instance claim 47 is dependent on claim 25. Applicants have not amended claim 25 along with the other claims. Thus Claims 25 still reads on the originally rejected composition.

Upon review and reconsideration in view of Applicants' amendments, claims 19, 20 are remain rejected under 35 U.S.C. §102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1). Claims 19 as written is simply drawn to an rAAV vector comprising at least one cis-acting heterologous transcriptional regulatory element, wherein the heterologous transcriptional regulatory element is a promoter. The limitation "is capable of regulating" does not impart any structural information to the claimed rAAV vector comprising a transcriptional regulatory element. Thus any AAV vector that comprises a cis-acting regulatory element will read on the instant claim.

Engelhardt et al. (U.S. Pat. No. 6,436,392 B1) discloses an rAAV, AV.GFP3ori (see Figure 14 A, and example 1) which is an rAAV comprising a CMV promoter. The rAAV was generated from the AAV recombinant shuttle vector, pCisAVGFP3ori (see figure 1 and b). Expression of the GFP gene was achieved by the CMV promoter/enhancer and SV40 polyadenylation sequences (see column 25, lines 53-60). Thus the instantly claimed composition comprising an AAVwith at least one cis-acting heterologous transcriptional regulatory element which is functional in a host cell is anticipated.

The rejection claims 1, 9, 19, 20, 46, 47, 58 and 59 under 35 U.S.C. 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology 1998) **is maintained** for reasons of record.

Applicants argument is that the AAV vectors disclosed by Rendahl et al. work in an operon like system and that the CMV promoter on the rAAV-tTA vector controls the expression of tTA and not erythropoietin on the other rAAV vector. In this system expression of erythropoietin is regulated by tetracycline.

Applicants' arguments have been fully considered but fail to be fully persuasive. Although it is appreciated that the goal of the Rendal et al. reference was to create a drug inducible system the reference still discloses the introduction of two AAV vectors into a cell. Thus the reference discloses the one AAV vector comprising a CMV promoter and the other AAV vector comprising a therapeutic gene product. In figure 2 C the tetracycline treated group at 16 or 18 weeks shows that the erythropoietin levels have not fully returned to baseline level after treatment with tetracycline and neither has the hematocrit level returned to base line after treatment with tetracycline which shuts off the minimal promoter. The reference discloses that that the AAV constructs forms concatemers when introduced into the cells (see page 760, column 1, 1st paragraph). Thus it is possible that low level of erythropoietin is expressed from the CMV promoter, resulting in the above base line level of the hematocrit seen in Figure 2C.

In this instance claim 47 is dependent on claim 25. Applicants have not amended claim 25 along with the other claims. Thus Claims 25 still reads on the originally rejected composition.

Claims 19 as written is simply drawn to an rAAV vector comprising at least one cis-acting heterologous transcriptional regulatory element, wherein the heterologous transcriptional

regulatory element is a promoter. The limitation "is capable of regulating" does not impart any structural information to the claimed rAAV vector comprising a transcriptional regulatory element. Thus any AAV vector that comprises a cis-acting regulatory element will read on the instant claim. The rAAV-tTA vector of the Rendahl et al. reference would read on the instantly claimed composition of claim 19 and 20.

The system disclosed by Rehndahl et al. comprises a CMV promoter (cis-acting regulatory element) which effects transcription of the tTA (which is located cis of the CMV promoter) and through the expression of tTA does the cis-acting regulatory element effect the transcription of the gene located on the second rAAV. Rehndahl et al. discloses the *in vivo* regulation of gene expression following co-injection of two separate recombinant adeno-associated virus vectors, one encoding an inducible murine erythropoietin transgene (a therapeutic gene) and the other a transcriptional activator, directly into the skeletal muscle of adult immunocompetent mice. Construct one (rAAV-CMV-tTA) comprises the tetracylince responsive transactivator and the mouse protamine polyadenylation site. Vector two (rAAV-(tetO)7-minCMV-mEPO) tetracycline responsive element reiterated 7 times regulating the minimal CMV promoter bovine growth hormone polyadenylation site. In this instance the expression tTA from one AAV construct regulates the expression of the inducible murine erythropoietin transgene that is found on the other AAV construct. The CMV promoter is functional in a host cell. The vectors are expressed in the same cells indicating that these cells comprise both AAV constructs. Therefore, the instant invention remains anticipated by Rendahl et al.

Double Patenting

The rejection of claims 1, 9, 46 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,436,292 **is withdrawn** in view of Applicants amendments to the claim. The claims are now drawn to a composition comprising of two rAAV constructs in which one of the constructs contains the entire open reading for a therapeutic gene construct.

The rejection of claims 47 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,436,292 **is maintained** because in this instance claim 47 is dependent on claim 25. Claim 25 has not been amended by Applicants along with the other claims. Thus Claims 25 still reads on the originally rejected composition. The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claim 1). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 9, 11, 46 and 47). Engelhardt et al. disclose a host cells comprising at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). The second DNA comprising a portion of an ORF operably linked to a promoter (see claim 9 and figure 14A, figure 19B column 3, lines 20-42). The promoter on vector 1 is responsible for the transcriptional regulation of the portion of the ORF gene product on the second vector. Without the concatamer formation the gene product on the second vector would not be transcribed in a host cell. The promoter on vector 1 is responsible for the transcription of

the gene product on vector 2. Therefore, the instant invention remains anticipated by Engelhardt et al.

New rejections in view of applicants amendments to the claims:

Claim Objections

Claims 63 and 66 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are objected to because they fail to further limit the parent claims which are compositions.

Claims 64 and 67 are objected to because of the following informalities: The claims are dependent on an objected claim. Appropriate correction is required.

Conclusion

Claims 60, 61 are allowable.

Claims 1, 9, 19, 20, 46, 47, 58 and 59.

Claims 63, 64, 66 and 67 are objected to.

Applicant is reminded that it is Applicants responsibility to amend all claims that may be entitled to rejoinder at a later date once allowable subject has been indicated. This includes claims that are drawn to non-elected inventions but that may be entitled to rejoinder either through linking claims practice or through the rejoining of product and process claims. Applicant is advised that a rejoinder of claims is possible at a later date if the product is

eventually found patentable. Guidance on treatment of product and process claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b) is set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86.

> To facilitate examination under § 103, where product and process claims are presented in the same application, applicant may be called upon under 35 U.S.C. § 121 to elect claims to either the product or process. The claims to the non-elected invention will be withdrawn from further consideration. However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from or otherwise includes all the limitations of an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of

such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 11/14/05